Chapter

Introductory Chapter: The Emerging Corner of the Omics Studies for Rational Drug Design

Arli Aditya Parikesit

1. Introduction

1.1 Structural bioinformatics contributions in -omics studies

The Acceleration of COVID-19 research in Proteomics and Transcriptomics studies occurred swiftly due to the massive amount of investment and advances in biomanufacturing [1, 2]. Moreover, the repurposing drug research has elicited remdesivir as the FDA-approved drug for COVID-19, despite mixed result from the WHO solidarity trial [3]. More drug leads are also currently undergoing clinical trial as well. This rapid development in the rational drug design is strongly associated with the field of structural bioinformatics. As for now (Early December 2020), there are more than 600 deposited SARS-CoV-2 Protein structures in the PDB (per December 2020, in the http://www.rcsb.org). They are SARS-CoV-2 Proteins with various conformations, and bindings with various ligands [4]. Hence, those proteins structures and their annotated functions are currently subject of the extensive COVID-19 drug development along with hefty investment from the pharmaceutical companies. However, in the other side of the story, non-protein biomolecular structures are currently still off the radar. There are only handful of initiatives for the COVID-19 transcriptomics-based drugs [5–7]. However, drug-based transcriptomics initiatives in canceromics are more mature. Breast cancer transcriptomics-based leads are currently under development [8–10]. That particular progress could be elicited due to the application of structural bioinformatics method for prediction the 2D and 3D model of the nucleic acids [11]. However, massive clinical applications still in favors for the proteomics-based drugs due to the stability of the bioassay experiments. In the area of natural products computation, the only realistic approach is still the proteomics-based one. For instance, propolis, as a resinous material from bees, was a subject of intensive molecular simulation research for its respective compounds constituency as diabetes drug candidates [12]. Hence, the same material also employed for the possibility as COVID-19 leads compound [13]. Moreover, various secondary metabolite sources were also investigated as drug candidates with the molecular simulation research, such as ayurvedic plants of India, and various sources of Chinese herbal medicine [14–18]. In this regard, bioinformaticians should proceed with mindful and prudent manner on the deployment of the molecular docking method as there are validation issues that should be resolved before working on the samples [19, 20]. That includes the utilization of the docking decoys, reiterations of Tc-PLIF value, cross-docking, redocking of the attached ligand, and the refinement of the RMSD parameter [21–25]. However, the easiest validation method is the ligand redocking, provided the structure is exist in the PDB repository. The decoy deployment is the most computationally extensive of all, albeit of its high

accuracy [26]. In this end, the measurement of the computational cost should be taken into consideration when applying molecular simulation is needed [27].

2. Pharmacogenomics and personalized medicine

Although it is still in its infancy, currently there is research that investigates the tendency that certain population group will be more vulnerable to COVID-19. For instance, Population with gene pool of Neanderthals was predicted to be vulnerable considerably [28]. In Indonesia, pharmacogenomics study has elicited correlation between anti-tuberculosis drug-induced liver injury (AT-DILI) severity and NAT2 phenotypes [29]. Moreover, expression of Long non-coding RNA (lncRNA) in diabetic patient is a useful lead for the progression of the epigenetic repertoire in the human cell [30]. Then, Molecular genomic is playing important role to annotate the cardiac function analysis [31]. The 7-day regiment deployment of the malaria drug primaquine is tolerated for patient with normal level of glucose-6-phosphate dehydrogenase (G6PD). Moreover, the resistance tendency of certain population group against malaria parasite has been observed as well [32]. Cancer is one of the most extensively studied disease in the pharmacogenomics field, in the light of the intensive computational biology tools, as tendencies for prevalence were elucidated in different races [33, 34]. Thus, the progress of epigenetics research has leveraged the pharmacogenomics field with various findings of biomarkers for cancer [35]. The various progresses in the pharmacogenomics field have shown that the molecular mechanism of diseases is beginning to be uncovered accordingly, especially with the development of epigenetics marker database [36]. Bioinformatics also play important role in annotating pharmacogenomics data, especially for the development of the genomics database and the disease-outcome prediction methods [37].

3. Metabolomics and disease biomarkers

The forefront of the metabolomics research is mainly the standard instrument in the analytical biochemistry such as HPLC and GC–MS, and also some supporting organic chemistry instrumentation such as C-NMR, H-NMR, UV, and IR [28–30, 38–40]. However, the deployment of the data science approach in interpretation of the metabolomics data enables the analysis of the large data sets, and eventually the data annotation in the biological database [41, 42]. Natural products research is one of the most dynamic fronts in the metabolomics research. Herbal medicine clinical trial toward COVID-19 patients show acceptable result for patients with mild symptoms, provided that the standard therapy still apply [43–45]. Moreover, secondary metabolite could serve as disease biomarkers. Insulin-resistant individuals will have decreased serum level of glycine, and also poor biotin metabolism [46]. Currently, probiotic metabolites are undergone extensive research to determine their possible anti-SARS-CoV-2 properties [47]. Propolis studies are also focused on the metabolomics side in order to provide sufficient data to the structural bioinformatics research, especially to determine the inhibitory activities against the SARS-CoV-2 virus [48–51]. Up to today, there are still limited number of the approved natural product based drugs, such as aspirin, penicillin, and taxol [52]. Bioinformatics research has been optimized to develop a more comprehensive biological conclusion in natural product chemistry, such as the annotation of naringin role in cancer, bioactive compounds of *Zingeber officinale,*

and caffeine-aspirin interaction [53–55]. So more efforts should be elicited to improve the completeness of the natural products library, mainly to supplement the standard chemical compounds library such as Pubchem, and drug database such as drugbank. Hence, biomarkers could be elicited not only as small organic molecules, but also as larger biomolecules. For instance, the insulin level is one of the indicator of the diabetes progression, and indicator for the therapeutic options available [56]. Diabetic biomarker could be manifested as non-coding RNA as well [57, 58].

4. Medicinal chemistry and drug design in omics study

The metabolomics study is definitely inseparable from medicinal chemistry due to their overlapping domain [59]. The development of the metabolomics library enables the construction of the rich chemical-structures library, as well as their respective functional groups from the natural products [57–62]. Custom-made library will supplement the existing libraries, such as the pubchem, drugbank, and KEGG database [63–65]. In this regard, the availability of the functional-groups library will support the fragment-based drug design, where specialized algorithm was devised to inhibit every corner of the protein's cavity [66, 67]. Hence, the main challenge of this approach will be in the medicinal chemistry perspective, when extrapolating the in silico research into the in vitro one become necessary. Synthesizing custom-made compounds from fragment library will not be straightforward due to the special reaction condition needed, the existence of the new structural backbone, and the availability of the chemical regents [68]. In this end, the current standing of the medicinal chemistry field is still depend upon the derivatization of the current structural library of compounds, in order to develop new lead with feasible reaction conditions [69]. Metabolomics plays dominant role in developing such library. One of the application of this particular approach is the development of ceftaroline, which is a fifth-generation broad-spectrum cephalosporin antibiotic [70].

5. Outlook

Parallelization in the Drug Biomanufacturing with incremental optimization will facilitate the pipeline of therapeutic agent development [71, 72]. Such biomanufacturing efforts will be enhanced with the implementation of Artificial Intelligence (AI) for massive drug screening that could be beneficial for multi-components drug lead such as herbal medication, and machine-learning based implementation for such pipelines has been devised accordingly in COVID-19 leads development [73–76]. The extensive utilization of the common data science methods in bioinformatics, such as machine learning, will eventually provide insight that the management of life sciences data requires more than just becoming application users [77]. Massive automation efforts in the field of life sciences will eventually push forward with the inevitable integration with formal sciences, namely with both computer science and data science [78]. In this end, Bioinformatics will play important role to manage the experimental data from the life sciences lab [79]. For instance, utilization of the SUPERFAMILY and Gene Ontology database for annotating the protein domain expression of the *Plasmodium sp.* parasite could be a doable venue [80, 81]. Thus, the promises that already delivered by the omics studies will eventually shed light to the current state of the COVID-19 pandemic (per December 2020), and could elicit various therapeutic options for many more

infectious diseases. However, non-communicable disease such as various types of cancer and diabetes will remain a challenging task to resolve as they invoke deep understanding of the human immunological system. It involves the utilization of the immunoinformatics tools that proceed beyond this chapter [82, 83]. Hence, it should be reminded that the basic sciences behind the omics studies could not be overlooked. Medicinal chemistry, biochemistry, molecular biology, biomedicine and biotechnology will remain important, as well as emerging sciences such as bioinformatics and data sciences.

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